Feasibility and safety of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis

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Objective: **Chronic cerebrospinal venous insufficiency (CCSVI) is a recently discovered syndrome mainly due to stenoses of internal jugular (IJV) and/or azygos (AZ) veins. The present study retrospectively evaluates the feasibility and safety of endovascular treatment for CCSVI in a cohort of patients with multiple sclerosis (MS).**

Methods: **From September 2010 to October 2012, 1202 consecutive patients were admitted to undergo phlebograpy ± endovascular treatment for CCSVI. All the patients had previously been found positive at color Doppler sonography (CDS) for at least two Zamboni criteria for CCSVI and had a neurologist-confirmed diagnosis of MS. Only symptomatic MS were considered for treatment. Percutaneous transluminal angioplasty was carried out as an outpatient procedure at two different institutes. Primary procedures, regarded as the first balloon angioplasty ever performed for CCSVI, and secondary (reintervention) procedures, regarded as interventions performed after venous disease recurrence, were carried out in 86.5% (1037 of 1199) and 13.5% (162 of 1199) of patients, respectively. Procedural success and complications within 30 days were recorded.**

Results: **Phlebography followed by endovascular recanalization was carried out in 1999 patients consisting of 1219 interventions. Balloon angioplasty alone was performed in 1205 out of 1219 (98.9%) procedures, whereas additional stent placement was required in the remaining 14 procedures (1.1%) following unsuccessful attempts at AZ dilatation. No stents were ever implanted in the IJV. The feasibility rate was as high as 99.2% (1209 interventions). Major complications included one (0.1%) AZ rupture occurring during balloon dilatation and requiring blood transfusion, one (0.1%) severe bleeding in the groin requiring open surgery, two (0.2%) surgical openings of the common femoral vein to remove balloon fragments, and three (0.2%) left IJV thromboses. The overall major and minor complication rates at 30 days were 0.6% and 2.5%, respectively.**

Conclusions: **Endovascular treatment for CCSVI appears feasible and safe. However, a proper learning curve can dramatically lower the rate of adverse events. In our experience, the vast majority of complications occurred in the first 400 cases performed. (J Vasc Surg 2013;58:1609-18.)**

Multiple sclerosis (MS) is a chronic and debilitating disease of the central nervous system characterized by the presence of scattered demyelinization plaques in the brain and/or the spinalcord.[1,2] Recently, the possibility has been raised that MS is associated with a chronic cerebrospinal venous insufficiency (CCSVI), a syndrome characterized by stenoses or obstruction of the internal jugular vein (IJV), brachiocephalic veins, azygos vein (AZ), and others.[3-7] Venous abnormalities can be present in several different combinations, and even two or more vessels can be involved in the same patient. In order to evaluate vein pathologies, different imaging modalities such as Doppler sonography (in the form of duplex scanning), magnetic resonance venography, or selective phlebography have been used, with venous disease correspondence among these tools being controversial in many cases.[8,9] Zamboni et al, using extracranial and transcranial sonography, established five ultrasound venous hemodynamic criteria that were able to distinguish MS patients from controls with 100% sensitivity and specificity.[10] A high prevalence of obstructive lesions has been found by some groups of MS patients compared with a low prevalence in healthy controls.[11-14] On the contrary, prevalence of such venous abnormalities has been reported to be dramatically lower in other studies.[15-20] However, this variability could be the result of differences in technique, training, experience, or criteria used.[21,22] To ensure a high reproducibility and accuracy between centers, recommendations for a protocol for duplex scanning has been recently published by the Intersociety Committee of the Consensus Conference on Practical Guidelines for the investigation and screening of CCSVI.[23]

Angioplasty is the treatment of choice for lesions producing venous disease. Nowadays, a few reports have been reported on endovascular treatment of CCSVI

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2013.05.108

patients with MS.[23-28] The aim of the present study is to retrospectively evaluate the feasibility and safety of phlebography and endovascular treatment for CCSVI in a cohort of patients with MS.

METHODS

Between September 2010 and October 2012, a total of 1202 consecutive patients were admitted to undergo phlebography ± endovascular treatment for CCSVI. Feasibility and safety of percutaneous transluminal angioplasty were retrospectively evaluated. All patients were previously diagnosed with CCSVI at color Doppler sonography (CDS) according to Zamboni score[10] and also had a neurologist-confirmed diagnosis of MS.[29] Only symptomatic MS were considered for treatment. The indication for venography and subsequent endovascular treatment was the presence of at least two out of five parameters of the Zamboni score (Table I).[23] Before the intervention, all participants completed questionnaires or brief interviews assessing medical history, medication use, parental psychopathology, demographics, psychiatric symptoms, alcohol and drug use, and cognitive status. The Mini Mental State Examination was performed to globally test basic cognitive functions.[30] The Kurtzke Expanded Disability Status Scale (EDSS) was performed in order to assess disability in MS patients.[31] The characteristics of the study population are summarized in Table II.

The study received institutional review board approval, and all participants gave their informed consent. All patients were treated in an outpatient basis by a single team of neurologists and vascular surgeons (Brain Flow Team). All interventions were performed at two different institutes by the same physician (T.L). In order to facilitate selective study of the left ascending lumbar veins, a tributary of the left common iliac vein, left groin, was preferred, when possible, and an 8- or 10F, 12-cm-long sheath (Terumo Medical Corporation, Elkton, Md) was introduced under local anesthesia in the common femoral vein. Venous puncture was carried out with a standard Seldinger technique. CDS guidance at the time of vein puncture was not used routinely but for difficult accesses only (ie, presence of scars at the groin, obesity, etc). Patients were administered either oral sedation with bromazepam (Bromazepam; Mylan Generics, Milan, Italy) or intravenous conscious sedation with midazolam hydrochloride (Midazolam; Mylan Generics) and were continuously monitored for heart and oxygen saturation. All patients received intravenous hydration 3 hours before, during, and immediately after the procedure.

A 6F, 100-cm-long, multipurpose catheter (Cordis Co, Miami, Fla) was selected first to cannulate both IJVs and left ascending lumbar veins. The multipurpose catheter was also used for the AZ; in those cases where catheterization of the AZ proved difficult with the multipurpose catheter, a 5F Cobra C1, 100 cm long (Cordis Co) was preferred. Finally, in some patients, selective study of the left IJV was achieved using a 6F, 100-cm-long right coronary catheter (Cordis Co).

Table I. Color duplex sonography criteria for CCSVI according to Zamboni et al[23]

CCSVI criteria
1. Reflux in the IJV and/or VV.
2. Reflux in the intracranial veins.
3. High-resolution B-mode: evidence of IJV stenosis and/or other B-mode anomalies.
4. Absence of flow in the IJV and/or VV.
5. CSA sitting > supine in the IJV.

CCSVI, Chronic cerebrospinal venous insufficiency; *CSA,* cross-sectional area; *IJV,* internal jugular vein; *VV,* vertebral vein.

Table II. Study population

Male	547 (45.5)
Female	655 (54.5)
Age, years	35 (18-78)
MS duration	11.3 (0.5-43)
MS form	
RR	584 (48.6)
SP	431 (35.9)
PP	112 (9.3)
Unknown	75 (6.2)

PP, Primary progressive; *RR,* relapsing remitting; *SP,* secondary progressive. Data are presented as number (%) or mean (range).

Phlebography was carried out at different levels in the IJV in every patient. Specifically, 5 mL of diluted iodine contrast (Visipaque; Amersham Health AS, Oslo, Norway) was injected manually with the tip of the catheter placed 10 cm above the IJV outlet (J2 level) as well as 8 to 10 cm above it (J3 level).[10] Antero-posterior and ipsilateral anterior oblique views were obtained for both IJVs in all patients. Two views (left anterior oblique at 30 degrees and lateral) were used to visualize the AZ. Angioplasty was carried out at the same time of phlebography. Prior to balloon dilatation, the patients were given unfractionated heparin (70 U/kg). A stenosis greater than 50% was considered the threshold for balloon dilatation. However, a luminal diameter reduction less than 50% in patients with a malformed valve, membrane, or septum at the vein outlet was also treated when associated with difficulty passing of the guidewire through the ostium and/or with flow abnormality such as reflux or stasis of the contrast medium. Type and number of vessels treated in the study population are reported in Table III. Stenoses and occlusions were treated using high-pressure balloons (Conquest PTA Dilatation Catheter, Atlas PTA Balloon Dilatation Catheter; Bard Peripheral Vascular, Tempe, Ariz) and/or standard (low-pressure) balloons (Admiral XtremeTM; Invatec, Bethelehem, Pa) either in the IJV and AZ. Balloons, chosen depending on diameter and characteristics of the vein lesion, were oversized approximately 20% more than the target vessel size (Fig 1). Standard balloons were selected first to treat stenoses in the AZ, preferring

Table III. Type and number of vessels treated in the study population

Type of intervention	*Patients, No. (%)*	*Procedures, No. (%)*
Endovascular treatment	1199	1219
Angioplasty	1185 (98)	1205 (98.9)
Angioplasty + stenting	14 (0.2)	14 (0.2)
Endovascular treatment of the right IJV	1140 (95)	1154 (94.7)
Endovascular treatment of the left IJV	1145 (95.5)	1158 (95)
Endovascular treatment of the AZ	935 (78)	947 (77.7)
Endovascular treatment of left anonimous vein	125 (10.4)	127 (10.4)
Endovascular treatment of left iliac vein	24 (2)	24 (2)

AZ, Azygos vein; *IJV,* internal jugular vein.

the use of the high-pressure ones after clear evidence of suboptimal dilatation only. High-pressure balloons were always chosen first for IJV angioplasty. At the beginning of our experience where high-pressure balloons were not still available in the market, two ordinary balloons placed at the outlet of the IJV were inflated simultaneously (kissing balloon technique; Fig 2). This relatively complex maneuver was made with the aim of achieving stronger dilatations at the vein outlet, which is particularly resistant to balloon opening, when standard balloon dilatation was suboptimal. Immediate recoil, evidence of twisting, and/or flow-limiting dissection in the IJV was treated with repeat angioplasty by means of prolonged balloon dilatations (5 minutes each). Angioplasty was terminated once all detectable lesions in the three target veins (left and right IJVs and AZ) were treated successfully or after three consecutive failing attempts at meliorating the blood flow through the injured vessel. Stent placement was carried out following inadequate response to previous attempts at balloon angioplasty only. In all patients, self-expandable bare stents (Protégé, EverFlex; eV3, Plymouth, Minn) were preferred to balloon-expandable ones.

Manual pressure on the groin was applied for a minimum of 10 minutes in all patients following removal of the introducer sheath. Patients were then observed and monitored in the recovery room for 30 minutes by a nurse. Afterward, they were sent back to the ward with the recommendation to keep very still in the bed for at least 2 hours. After a further 2 hours, the patients were allowed to ambulate under strict observation and to leave the hospital if they were clinically stable without any abnormalities of their vital signs. Recommendation about staying in a local hotel for the following 12 hours was made to all patients. The following morning, most of the patients underwent CDS of the neck veins. General conditions and punctured groin were also carefully evaluated.

Postoperative antithrombotic prophylaxis was scheduled as follows: 4000 U of low-molecular-weight heparin every 12 hours for 15 days (it was prolonged to 40 days after the first 112 cases); 100 mg of mesoglycan (Prisma; Mediolanum Farmaceutici, Milan, Italy) every 12 hours + 100 mg of aspirin daily for the following 3 months; and finally, aspirin 100 mg daily for the following 6 months.

Patients in whom a stent was implanted received warfarin for the first 6 months with the recommendation to keep the international normalized ratio between 2 and 3, then aspirin 100 mg + 75 mg clopidogrel (Plavix; Bristol Meyers Squibb, New York, NY) daily for the following 6 months, and finally, 100 mg of aspirin, indefinitely. The patients were seen at our center or alternatively were contacted by phone or by e-mail at 7 and 30 days from the procedure. In case of procedure-related problems, the patients were invited to contact the hospital at any time. All of the patients were scheduled to have both clinical and neurological evaluation as well as CDS of the neck veins at 2, 6, 12, and 18 months at our center.

Study end points and definition. The primary end point was the combined number of complications at 30 days after the endovascular treatment. Procedural success and technical success were measured as additional primary end points. Procedural success was defined as capability of performing selective catheterization of the three target vessels, followed, if necessary, by their balloon dilatation, whereas technical success was regarded as achievement of normal venous return in the three target vessels. Failure to perform the procedure, regardless of whether the outcome was presence or absence of a complication, was defined as the inability to gain access with the introducer sheath in the vein circulation, to engage all target vessels with the diagnostic catheter, or to perform, whenever indicated, target vessels balloon dilatation. Failure to achieve normal venous return, regardless of whether the outcome was presence or absence of a complication, was defined as persistence in $\geq$1 target vessel or $\geq$1 of the following conditions: (1) occlusion or residual stenosis >50%; (2) reflux or stasis of contrast medium; (3) difficulty passing of the guidewire through the target vessel.

The secondary end point was the combined number of minor complications during the first 30 days after the endovascular treatment. Transient chest pain, neck pain, and/or headache were regarded as typical symptoms after the procedure and were not registered as adverse events.

RESULTS

Stenosis >50% and/or other venous problems such as flow abnormality or difficulty passing of the guidewire with evidence of a vessel narrowing <50% were seen in 85.7% and 16.3% of the right IJV and 85.3% and 16.9% of the left IJV, respectively. No evidence of any disease was registered in 5% and 4.5% of the right and left IJV, respectively. Significant disease of the AZ, regarded as evidence of stenosis >50% and/or other venous pathology with a vessel stenosis <50% was registered in 935 patients (78%).

Venography followed by endovascular recanalization was carried out in 1994 patients in 1214 procedures. In five additional patients (five procedures), the decision to carry out the interventional treatment was solely taken after

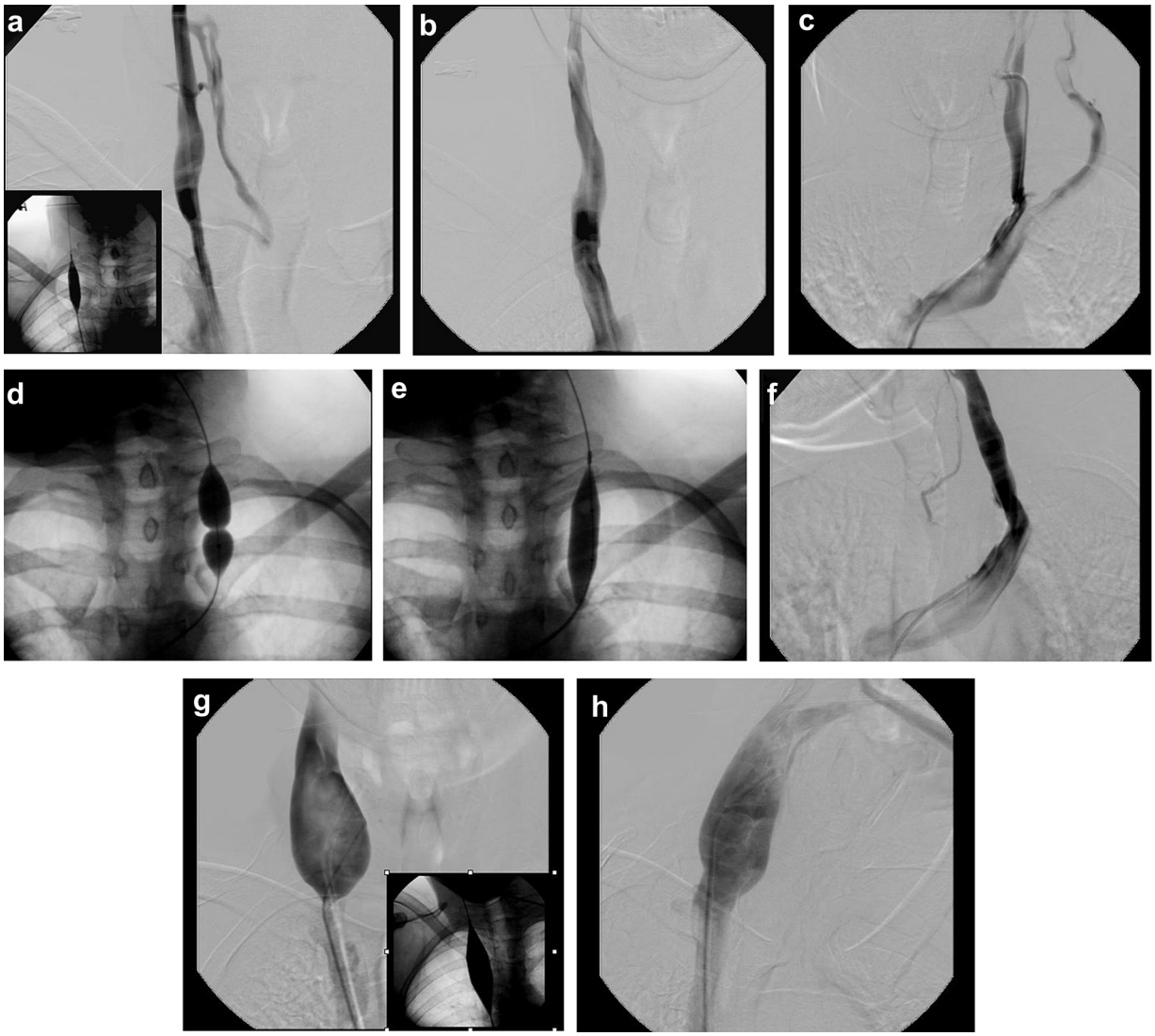

Fig 1. Right internal jugular vein (IJV) balloon angioplasty at the vein outlet **(a)**. No evidence of collateral vessels after complete reopening of the vein **(b)**. Narrowing of the left IJV at the level of the ostium **(c)**. Angioplasty with a standard balloon proved ineffective due to the presence of a highly resistant stenosis **(d)**. The standard balloon was changed for a high-pressure one that allowed full dilation of the vein lesion **(e** and **f)**. Right IJV stenosis/occlusion; balloon dilatation **(g)** with subsequent significant improvement of the vein outflow **(h)**.

venography because of uncertain diagnosis of CCSVI at CDS. Three patients (three procedures) were not treated endovascularly because no significant disease in at least one IJV was seen at phlebography, despite evidence of CCSVI at CDS. Therefore, the endovascular treatment was performed in a total of 1199 (99.8%) patients consisting of 1219 (99.8%) procedures.

Balloon angioplasty alone was carried out in 1185 (98.8%) patients and in 1205 (98.9%) procedures, whereas additional stent placement was required in the remaining 14 patients (1.2%) in 14 interventions (1.1%) following unsuccessful attempts at AZ dilatation. No stents were ever implanted in the IJV.[23] Primary procedures, regarded as the first balloon angioplasty ever performed for CCSVI, and secondary (reintervention) procedures, regarded as interventions performed after a venous disease recurrence, were carried out in 86.5% (1037 of 1199) and 13.5% (162 of 1199) of patients, respectively. Specifically, 1.7% (20) of patients who underwent reinterventions had been previously treated at our institute, whereas 11.8% (142) were treated elsewhere. Secondary procedures were all carried out after at least 6 months from the previous endovascular intervention. All 1199 patients underwent balloon angioplasty of one or more target vessels and at least two balloons were employed (mean, 2.8 balloons; range, 2-9 balloons) in every case. Standard balloons of 8 to 12 mm

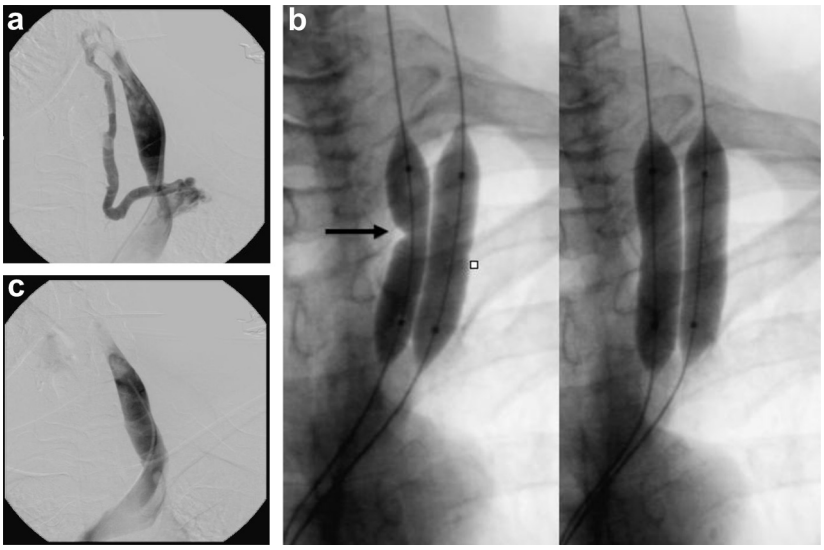

Fig 2. Left internal jugular vein (IJV) narrowing at the vein outlet. A large collateral vessel draining at the junction between the subclavian and the anonymous veins is also seen **(a)**. Balloon angioplasty with the kissing-balloon technique. Following dilatation of both balloons **(b)**, complete reopening of the vein as well as disappearance of the large collateral vein is seen **(c)**.

in diameter and 20 to 40 mm in length were generally used in the mid (J2) and distal (J3) portion of the IJV, whereas high-pressure balloons of 10 to 26 mm in diameter and 20 to 40 mm in length were used more proximally, mostly at the vein outlet (J1). Standard balloons ranging from 5 to 12 mm in diameter and 20 to 60 mm in length and/or high-pressure balloons ranging from 10 to 14 mm in diameter and 20 to 40 mm in length were chosen for the treatment of the AZ. Standard balloons were selected first to treat stenoses in the AZ, reserving the use of the high-pressure ones solely after clear evidence of suboptimal dilatations. A single stent of 12 or 14 mm in diameter × 40 mm in length was deployed in 13 patients. In one patient, two (overlapping) stents (one 14 mm × 40 mm and one 12 × 20 mm) were used in the same session. All but one were released at the distal segment of the AZ arch where a severe twisting of the vein was present. In one patient, a 12-mm × 40-mm stent was implanted at the vein ostium (Fig 3, *a-c*). Four patients presented with a left innominate vein hypoplasia with evidence of blood flow drainage into the right atrium through a left persistent superior vena cava and the coronary sinus. Selective catheterization of the left IJV was then carried out through the coronary sinus and the left persistent superior vena cava as previously reported by our group.[22] Two patients underwent inadvertent catheterization of the left common femoral artery; percutaneous closure devices were used without further sequelae. Out of 1199 patients, 1177 (98.2%) were discharged at 4 hours from the intervention. Nineteen (1.6%) patients were discharged the following day, whereas three (0.3%) patients were discharged at 2 days, 3 days, and 7 days, respectively. Follow-up with CDS was completed at 2, 6, and 12 months by 1141 out of 1199 (95.2%), 1024 out of 1129 (90.7%), and 874 out of 1026 (85.2%) patients, respectively. The overall rate of CSSVI, regarded as either persistence or recurrence of ≥two Zamboni criteria following percutaneous transluminal angioplasty, was 11.8% at 6 months and 19.1% at 1 year, respectively.

Primary end points. Major complications included one (0.1%) AZ rupture occurring during a standard balloon dilatation with a 10- × 20-mm high-pressure balloon. The patient had sudden unexpected severe hypotension requiring blood transfusion and vital parameters stabilization. Selective phlebography showed a 2-cm vein pseudoaneurysm close to the AZ ostium causing severe bleeding in the mediastinum. A self-expandable bare stent was promptly deployed (EverFlex; eV3, Plymouth, Minn) at the origin of the AZ followed by coil embolization of the sac. Indeed, a 4F Cobra catheter was advanced through the meshes of the stent, and three 4 × 4 fibered coils (Vortex; Boston Scientific, Natick, Mass) were carefully packed within the lesion (Fig 3). The patient did well and was discharged after 7 days. There were two (0.2%) balloon deflagrations, both occurring during a prolonged dilatation for a very though stenosis in the left IJV. Both devices were high-resistance balloons of 18 × 20 mm. Unfortunately, it was not possible to remove them through the 10F introducer sheath in the left groin. Both patients were treated in the cath lab at the time of the endovascular intervention by surgical opening of the left common femoral vein. After careful removal of all the fragments, vein suturing was obtained; the endovascular intervention was then continued in the standard fashion with no evidence of further complications. Both patients were discharged home the following day in good general conditions. One

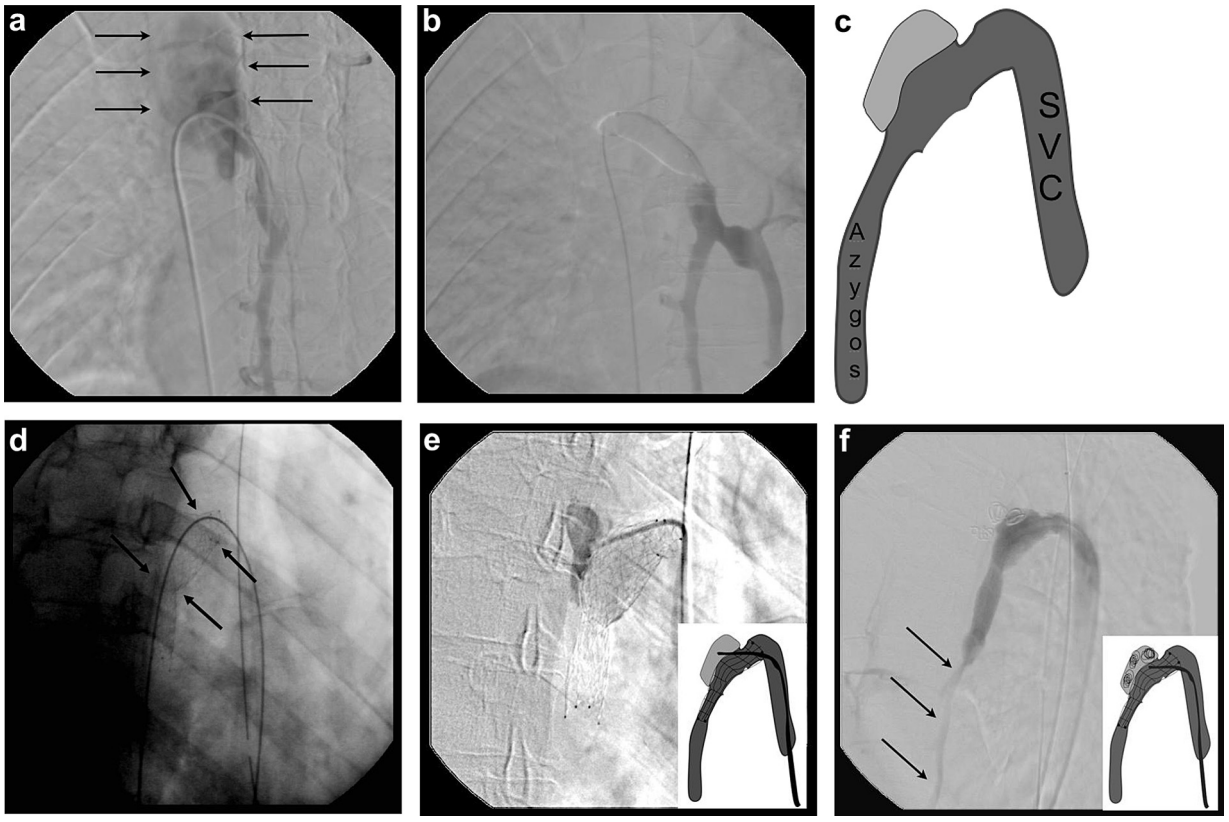

Fig 3. Azygos vein (AZ) rupture following balloon angioplasty at the vein outlet. Subtraction angiography shows massive extravasation of contrast medium (*arrows*) within the mediastinum **(a)**. A standard balloon is placed close to the vein outlet and inflated at two atmospheres for 20 minutes in an effort to stop the vessel from bleeding **(b)**. After balloon removal, complete cessation of bleeding is noted. However, a 3- × 3-cm pseudoaneurysm of the AZ (*arrow*) located at 2 cm from the junction with the superior vena cava is also seen **(c)**. Bare stent placement of the AZ **(d)** followed by coil embolization of the pseudoaneurysm. Coil embolization was performed using a 4F Cobra catheter with its tip advanced through the meshes of the stent **(e)**. Confirmation angiography shows good coil packaging of the sac with a preserved flow throughout the AZ. A vein spasm of the descending portion of the AZ is noted at the end of the procedure (*arrows*) **(f)**. *SVC,* Superior vena cava.

(0.1%) severe bleeding at the groin requiring rehospitalization was reported. It was caused by occurrence of a vein wall tear, likely due to a traumatic introducer sheath advancement following a difficult left CFV puncture. The patient was readmitted 3 days after the discharge and successfully treated by open surgery. Three patients (0.3%) were found to have thrombosis in the left IJV within 30 days from the percutaneous transluminal angioplasty. They were readmitted due to occurrence of sudden pain in the neck. All thromboses were discovered at CDS obtained at 17, 19, and 23 days. The overall rate of major complications at 30 days was as low as 0.6% (7 of 1219). Of importance was that all major complications occurred during the first 400 cases treated (Table III). Procedural success was obtained in 1192 patients (99.2%) and 1212 (99.2 %) procedures. In fact, selective study of all target vessels was not possible in three (0.3%) and seven (0.6%) cases due to a vein agenesis (one left IJV and two AZ vein) and complete occlusion/thrombosis (two right and left IJVs) following previous endovascular balloon dilatations, respectively. Technical success of the IJV was obtained in 1084 (90.4%) patients and 1104 (90.6%) procedures. Specifically, in 81 (6.8%) patients, a persistent stenosis >50% of at least one IJV was seen at confirmation phlebography. In all these patients, significant external compression (due to presence of surrounding structures such as muscles, carotid artery, or bones compressing the IJV at one or more vein sites) not responding to repeat and prolonged balloon dilatation was noted. Seven (0.6%) patients showed a residual stenosis >50% following percutaneous transluminal angioplasty, either at the vein outlet (three patients; two left and one right IJV) or in the distal portion (four patients; three left and one right IJV), whereas 17 (1.4%) showed persistent abnormal flow (five in the right and 12 in the left side). Finally, in the 10 (0.8%) patients presenting with agenesis or total occlusion of one target vessel, although the remaining target vessels were dilated

Table IV. Primary and secondary end points calculated at 30 days in a total of 1219 endovascular treatments

Adverse events	*Total, No. (%)*	*0-400, No. (%)*	*401-1219, No. (%)*
Primary end points			
Major complications			
Death	-		
Stroke	-		
Myocardial infarction	-		
Postprocedural venous thrombosis	3 (0.2)	3 (0.2)	-
Severe bleeding in the groin requiring open surgery	1 (0.1)	1 (0.1)	-
Vessel rupture requiring blood transfusion	1 (0.1)	1 (0.1)	-
Surgical opening of common femoral vein to remove balloon fragments	2 (0.2)	2 (0.2)	-
Total	7 (0.6)	7 (0.6)	-
Unsuccessful catheterization of all target vessels			
AZ	2 (0.2)	2 (0.2)	-
IJV	8 (0.7)	2 (0.2)	6 (0.5)
Procedural success	1209 (99.2)	396 (99)	813 (99.2)
Secondary end points			
Minor complications			
Mild contrast reaction	3 (0.2)	2 (0.2)	1 (0.1)
Transient cardiac arrhythmia	13 (1.1)	8 (0.7)	5 (0.4)
Puncture site bleeding or groin hematoma	10 (0.8)	7 (0.6)	3 (0.3)
Neck hematoma	2 (0.2)	1 (0.1)	1 (0.1)
Lung migration of a balloon fragment	1 (0.1)	1 (0.1)	-
Hemotimpanus	1 (0.1)	1 (0.1)	-
Common femoral artery pseudoaneurysm	1 (0.1)	1 (0.1)	-
Total	31 (2.5)	21 (1.7)	10 (0.8)

AZ, Azygos vein; *IJV*, internal jugular vein.
Complications have also been calculated before and after the first 400 procedures performed.

successfully, complete normalization of vein return from the brain or spinal cord to the heart could not be obtained.

Successful recanalization of the AZ was obtained in 911 (97.4%) out of 935 patients and 934 (97.4%) out of 958 procedures.

Secondary end points. A transient cardiac arrhythmia was reported in 13 (1.1%) cases. In four procedures, the tachyarrhythmias resolved within 2 hours, whereas in the remaining nine, it progressed to atrial fibrillation that required a 24-hour hospitalization before discharge. Ten (0.8%) slight bleeding or hematomas in the groin (seven needing further hospital care <12 hours and three >12 hours) with no clinical consequences, two slight right neck hematomas (0.2%) not requiring hospitalization, and one (0.1%) hemo-tympanum on the 25th day after discharge were also reported. In one (0.1%) patient, a fragment of a ruptured balloon migrated from the left IJV to the right pulmonary artery, thus requiring the use of a dedicated snare catheter (GoosNeck snare catheter; eV3) to retrieve it from the lung into the 10F introducer sheath. Finally, three (0.3%) mild contrast reactions occurred. All of them became evident within 2 hours from the endovascular intervention and were treated with antihistamine and intravenous fluid administration. One (0.1%) patient was readmitted at 3 days with signs of moderate hemoglobin depletion. The patient underwent computed tomography scan that showed a 1.2- × 1.8-mm left common femoral artery pseudoaneurysm, which was promptly excluded by coil embolization. At 30-day follow-up, the rate of minor complications was 2.5% (31 of 1219 procedures), whereas the overall rate of complications was 3.1% (38 of 1219 procedures; Table IV).

DISCUSSION

The present study was not intended to evaluate clinical outcomes of angioplasty in CCSVI patients but was focused on straight evaluation of the intraprocedural and short-term risks associated with this intervention. In our experience of more than 1200 patients performed over the course of 2 years, the rate of minor and major complications was in accord with those published so far in the literature.[25-29,32-36] No major contrast medium-related complications occurred. There was one AZ rupture leading to a massive bleeding within the mediastinum (Fig 3), whereas no severe bleedings from the IJVs were seen following percutaneous transluminal angioplasty. Indeed, in certain cases, it was possible to observe in the AZ and/or in the IJVs a slight bleeding after angioplasty with a small amount of contrast coming out and surrounding the vessels just at the site of ballooning. In fact, in a few patients, mostly those <25 years old, vein malformations at the vessel outlet have shown to be particularly resistant to balloon dilation, thus requiring multiple attempts at ballooning as well as a higher pressure of balloon inflation. In case of an inflation pressure greater than 28 and 22 atmospheres in 12- to 18-mm and 20- to 26-mm-diameter balloons, respectively, a tear in the vessel wall, as a result of sudden vein malformation disruption, may occur. Fortunately, in such a scenario, the low pressure

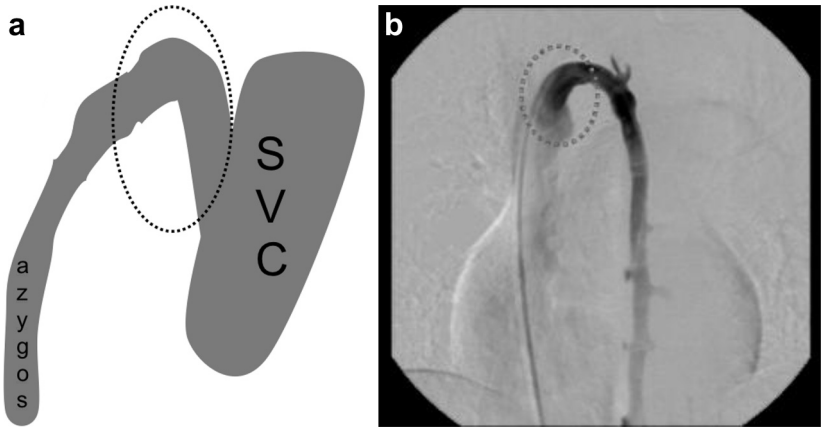

Fig 4. The proximal segment of the azygos vein (AZ), which is the portion between the vena cava and the azygous arch (within the circle), may lead to a massive bleeding into the mediastinum if it breaks during balloon dilatation **(a** and **b)**. *SVC,* Superior vena cava.

within the vein circulation as well as presence of a perivascular tissue surrounding both the IJV and the distal part of the AZ (arch and descending portion) prevent the blood from extravasating into the neighboring tissues (in rare cases, a limited amount of blood may slightly leak from the site of balloon dilatation with no clinical consequences). Nevertheless, the proximal segment of the AZ, which is the portion of the vein arising from the superior vena cava and extending up to the AZ arch, is not surrounded by any tissue[37]; if not promptly recognized, a rupture of the AZ or even a simple tear at this level following angioplasty is likely to lead to a massive bleeding into the mediastinum with subsequent risk of ipovolemic shock (Fig 4). In order to stop the vein from bleeding, the use of a stent, to be placed at the AZ origin, may be highly required. In our case, we released a bare stent at the site of bleeding followed by deployment of several fibered coils through the stent meshes. The use of a covered stent without the need of placing the coils would have been faster and easier, but it would have probably been at increased risk of thrombosis or in-stent restenosis in the long term. Moreover, no evidence of covered stent implantation in the AZ territory has been ever reported in the literature up to now. For this reason also, we preferred to avoid using a covered prosthesis in the AZ.

A very dreadful complication was the postangioplasty vein thrombosis, which accounted for a total of three cases; importantly, all of them occurred in the first 112 patients treated.

However, since we prolonged the time of heparin administration from 15 to 40 days, such a complication was no longer seen. Iatrogenic cardiac arrhythmia (followed by atrial fibrillation in nine cases) was the most common complication in our series. Potential iatrogenic causes of atrial fibrillation include cardiac and noncardiac surgery and administration of a variety of medications including bronchodilating beta-agonists, various nonprescription cold remedies, antihistamines, local anesthetics, and caffeine-containing beverages.[38] In our series, all cardiac arrhytmias developed during guidewire/catheter passage from the inferior to superior vena cava or at the time of balloon dilatation of the AZ. The presence of atrial fibrillation contributes to morbidity and mortality under a variety of circumstances. Thus, a rapid ventricular response secondary to the presence of atrial fibrillation can produce myocardial ischemia with resultant unstable angina or even myocardial infarction in a patient with underlying arteriosclerotic coronary artery disease.[39,40] Considerable attention should be focused on patients with history of myocardial infarction and/or congestive heart failure who undergo venous angioplasty for CCSVI. Another relatively common complication was the occurrence of bleeding and/or hematomas at the access site. It was mostly seen in those patients who discontinued bed rest due to rapid postoperative recovery of their walking capability. However, it is not possible to exclude that an inadvertent puncture of the arterial bed might have occurred during the attempts at femoral vein puncture, particularly in those cases where puncturing proved to be extremely difficult. Indeed, a main limitation of the present series is that no CDS evaluation of the venous access was obtained before femoral vein puncture. Actually, a proper preevaluation of the target vessel with CDS has been reported to reduce the rate of complications at the entry site.[41,42]

CONCLUSIONS

Our study, which is the largest interventional one ever carried out in such a population, confirms that the rate of adverse events following catheter angioplasty is reasonably low with low risk of serious adverse events. However, a proper learning curve seems to highly reduce the rate

of complications. In our experience, the vast majority of complications occurred in the first 400 cases performed.

AUTHOR CONTRIBUTIONS

Conception and design: TL, PO
Analysis and interpretation: TL, GB, ER
Data collection: GB, ER, VD, IF, RF
Writing the article: TL
Critical revision of the article: TL, FG
Final approval of the article: TL, PO
Statistical analysis: IF, ER
Obtained funding: TL, PO
Overall responsibility: TL

REFERENCES

1. Frohman EM, Racke MK, Raine CS. Multiple sclerosis-the plaque and its pathogenesis. N Engl J Med 2006;354:942-55.
2. Barnet MH, Sutton I. the pathology of multiple sclerosis: a paradigm shift. Curr Opin Neurol 2006;19:242-7.
3. Zamboni P. The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. J R Soc Med 2006;99:589-93.
4. Zamboni P, Lanzara S, Mascoli F, Caggiati A, Liboni A. Inflammation in venous disease. Int Angiol 2008;27:361-9.
5. Zivadinov R, Galeotti R, Hojnacki D, Menegatti E, Dwyer MG, Schirda C, et al. Value of MR venography for detection of internal jugular vein anomalies in multiple sclerosis: a pilot longitudinal study. Am J Neurorad 2011;32:938-46.
6. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
7. Singh AV, Zamboni P. Anomalous venous blood flow and iron deposition in multiple sclerosis. J Cereb Blood Flow Metab 2009;29: 1867-78.
8. Lee BB, Choe YH, Ahn JM, Do YS, Kim DI, Huh SH, et al. The new role of MRI (Magnetic Resonance Imaging) in the contemporary diagnosis of venous malformation: can it replace angiography? J Am Coll Surg 2004;198:549-58.
9. Schreiber SJ, Lurtzing F, Gotze R, Doepp F, Klingebiel R, Valdueza JM. Extrajugular pathways of human cerebral venous blood drainage assessed by duplex ultrasound. J Appl Physiol 2003;94: 1802-5.
10. Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'Ara S, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. J Neurol Sci 2009;282:21-7.
11. Zaniewski M, Kostecki J, Ziaja K, Urbanek T, Kuczmik W, Krzystanek E, et al. Endovascular surgery for the treatment of symptoms of multiple sclerosis. Preliminary report. Chirurgia Polska 2010;12:12-7.
12. Zamboni P, Menegatti E, Bartolomei I, Galeotti R, Malagoni AM, Tacconi G, et al. Intracranial venous haemodynamics in multiple sclerosis. Curr Neurovasc Res 2007;4:252-8.
13. Zamboni P, Consorti G, Galeotti R, Gianesini S, Menegatti E, Tacconi G, et al. Venous collateral circulation of the extracranial cerebrospinal outflow routes. Curr Neurovasc Res 2009;6:204-12.
14. Bartolomei I, Salvi F, Galeotti R, Salviato E, Alcanterini M, Menegatti E, et al. Hemodynamic pattern of chronic cerebrospinal venous insufficiency in multiple sclerosis. Correlation with symptoms at onset and clinical course. Int Angiol 2010;29:183-8.
15. Sundström P, Wåhlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. Ann Neurol 2010;68:255-9.
16. Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol 2010;68:173-83.
17. Centonze D, Floris R, Stefanini M, Rossi S, Fabiano S, Castelli M, et al. Proposed chronic cerebrospinal venous insufficiency criteria do not predict multiple sclerosis risk or severity. Ann Neurol 2011;70: 52-9.
18. Baracchini C, Perini P, Calabrese M, Causin F, Rinaldi F, Gallo P. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. Ann Neurol 2011;69:90-9.
19. Floris R, Centonze D, Fabiano S, Stefanini M, Marziali S, Del Giudice C, et al. Prevalence study of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: preliminary data. Radiol Med 2012;117:855-64.
20. Garaci FG, Marziali S, Meschini A, Fornari M, Rossi S, Melis M, et al. Brain hemodynamic changes associated with chronic cerebrospinal venous insufficiency are not specific to multiple sclerosis and do not increase its severity. Radiology 2012;265:233-9.
21. Menegatti E, Genova V, Tessari M, Malagoni AM, Bartolomei I, Zuolo M, et al. The reproducibility of colour Doppler in chronic cerebrospinal venous insufficiency associated with multiple sclerosis. Int Angiol 2010;29:121-6.
22. Zamboni P. Regarding "no cerebrocervical venous congestion in patients with multiple sclerosis. Intraluminal jugular septation". Ann Neurol 2010;68:969; author reply: 970.
23. Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound - recommendations for a protocol. Int Angiology 2011;30:571-97.
24. Lupattelli T, Benassi F, Righi E, Bavera P, Bellagamba G. Percutaneous transluminal angioplasty in a patient with chronic cerebrospinal venous insufficiency and persistent left superior vena cava. Phlebology 2012 November 15; [Epublication ahead of print].
25. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Gianesini S, Bartolomei I, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009;50:1348-58.
26. Zamboni P, Galeotti R, Weinstock-Guttman B, Kennedy C, Salvi F, Zivadinov R. Venous angioplasty in patients with multiple sclerosis: results of a pilot study. Eur J Vasc Endovasc Surg 2012;43:116-22.
27. Ludyga T, Kazibudzki M, Simka M, Hartel M, Swierad M, Piegza J, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010;25: 286-95.
28. Mandato KD, Hegener PF, Siskin GP, Haskal ZJ, Englander MJ, Garla S, et al. Safety of endovascular treatment of chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. J Vasc Interv Radiol 2012;23:55-9.
29. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
30. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
31. Kurtzke JF. Disability rating scales in multiple sclerosis. Ann N Y Acad Sci 1984;436:347-60.
32. Petrov I, Grozdinski L, Kaninski G, Iliev N, Iloska M, Radev A. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Endovasc Ther 2011;18:314-23.
33. Malagoni AM, Galeotti R, Menegatti E, Manfredini F, Basaglia N, Salvi F, et al. Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. Int Angiol 2010;29:176-82.
34. Siskin GP, Haskal ZJ, McLennan G, Dake MD, Haacke EM, McDonald S, et al. Development of a research agenda for evaluation of interventional therapies for chronic cerebrospinal venous insufficiency: proceedings from a multidisciplinary research consensus panel. J Vasc Interv Radiol 2011;22:587-93.
35. Zamboni P, Bertolotto A, Boldrini P, Cenni P, D'Alessandro R, D'Amico R, et al. Efficacy and safety of venous angioplasty of the extracranial veins for multiple sclerosis. Brave Dreams Study (Brain

Venous Drainage Exploited Against Multiple Sclerosis): study protocol for a randomized controlled trial. Trials 2012;13:183.
36. Vedantham S, Benenati JF, Kundu S, Black CM, Murphy KJ, Cardella JF, et al. Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010;21:1335-7.
37. Smathers RL, Buschi AJ, Pope TL Jr, Brenbridge AN, Williamson BR. The azygous arch: normal and pathologic CT appearance. AJR Am J Roentgenol 1982;139:477-83.
38. Mackstaller LL, Alpert JS. Atrial fibrillation: a review of mechanism, etiology, and therapy. Clin Cardiol 1997;20:640-50.
39. Crijns HJ, Tjeerdsma G, de Kam PJ, Boomsma F, van Gelder IC, van den Berg MP, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. Eur Heart J 2000;21:1238-45.
40. Behar S, Tanne D, Zion M, Reicher-Reiss H, Kaplinsky E, Caspi A, et al. Incidence and prognostic significance of chronic atrial fibrillation among 5839 consecutive patients with acute myocardial infarction. Am J Cardiol 1992;70:816-8.
41. Prabhu MV, Juneja D, Gopal PB, Sathyanarayanan M, Subhramanyam S, Gandhe S, et al. Ultrasound-guided femoral dialysis access placement: a single-center randomized trial. Clin J Am Soc Nephrol 2010;5:235-9.
42. Chen JY, Chang KC, Lin YC, Chou HT, Hung JS. Feasibility and accuracy of pre-procedure imaging of the proximal cephalic vein by duplex ultrasonography in pacemaker and defibrillator implantation. J Interv Card Electrophysiol 2004;10:31-5.

Submitted Jan 8, 2013; accepted May 28, 2013.